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TGF-beta and functional differentiation.

Smith GH.

*J Mammary Gland Biol Neoplasia*. 1996 Oct;1(4):343-52.Oncogenetics Section, National Cancer Institute, Bethesda, Maryland  
20892-1750, USA. SmithG@ltiblp.nci.nih.gov

A review of the pertinent literature suggests that TGF-beta 1 may play a multifaceted role in functional differentiation of mammary epithelium. Evidence for the expression of TGF-beta 1 RNA and the presence of functional TGF-beta 1 protein in differentiating mammary epithelial cells from a pregnant mouse has been recently reported. The specific role of mammary-epithelial-cell-produced TGF-beta 1 in the differentiating mammary gland is presently unclear. However, several possible functions are suggested from the following observations. Milk protein production is negatively regulated by exogenous TGF-beta 1 during gestational development of the gland but not during lactation. Consistent with reports linking TGF-beta 1 gene expression with mammary gland involution following lactation, overexpression of TGF-beta 1 in the differentiating secretory epithelium leads to premature programmed cell death in the absence of a negative effect on secretory epithelial cell proliferation. A role for TGF-beta 1 in cell cycle control and suppression of malignant progression independent from its inhibitory effect on epithelial cell growth has been demonstrated in keratinocytes. A similar function could provide protection against malignancy in proliferating mammary epithelium and account for TGF-beta 1 suppression of mammary tumorigenesis in transgenic mice overexpressing transforming growth factor alpha (TGF-alpha).

Publication Types:

- o Journal Article
- o Review



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Articles**The role of TGF-beta in patterning and growth of the mammary ductal tree.**

Daniel CW, Robinson S, Silberstein GB.

*J Mammary Gland Biol Neoplasia*. 1996 Oct;1(4):331-41.

Department of Biology, University of California, Santa Cruz 95064, USA. daniel@darwin.ucsc.edu

Evidence that transforming growth factor beta (TGF-beta) influences pattern formation in the developing mammary gland and negatively regulates ductal growth is reviewed. In the mouse, overexpression of TGF-beta transgenes during puberty reduces the rate of growth of the ductal tree and simplifies the pattern of arborization, while expression during pregnancy also interferes with lactation. Expression studies in the normal mouse gland indicate that TGF-beta is synthesized in the mammary epithelium, with the three isoforms showing somewhat different spatial and temporal distributions. Exogenous TGF-beta applied directly to the gland in situ inhibits epithelial cell division within hours, and strongly stimulates extracellular matrix synthesis over a longer time course. Normal human breast cells as well as certain breast cancer cell lines also secrete TGF-beta and are themselves inhibited by it, suggesting an autoregulatory feedback circuit, that in some cases appears to be modulated by estradiol. Taken together, the evidence suggests a model in which growth and patterning of the mammary ductal tree are regulated, at least in part, by TGF-beta operating through an autocrine feedback mechanism and by paracrine circuits associated with epithelial-stromal interactions.

## Publication Types:

- o Journal Article
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- o Review, Tutorial



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**Progesterone antagonists: tumor-inhibiting potential and mechanism of action.**

Michna H, Nishino Y, Neef G, McGuire WL, Schneider MR.

*J Steroid Biochem Mol Biol.* 1992 Mar;41(3-8):339-48.

Research Laboratories of Schering AG, Berlin, Fed. Rep. Germany.

A new approach for the treatment of breast cancer could be the use of progesterone antagonists. These compounds were originally developed for the inhibition of progesterone-dependent processes and have been shown to be effective in inhibition of nidation and interruption of pregnancy. Although the roles of progesterone and the progesterone receptor in control of cell growth remain unclear, it was found in progesterone receptor positive mammary carcinoma cell lines that the antiprogesterin, Mifepristone, had an inhibitory effect on cell growth and a growth-inhibiting action on the DMBA-induced mammary carcinoma of the rat. We have shown that the progesterone antagonists, Onapristone and ZK 112993, which possess a reduced antiglucocorticoid activity compared to Mifepristone, exert a strong tumor-inhibiting effect in a panel of hormone-dependent mammary tumor models. The effects of these compounds were in some systems superior to those of tamoxifen or high dose progestins and comparable to ovariectomy. Although prerequisites for their antiproliferative potency are an affinity to the progesterone receptor as well as a sufficient number of available receptors in the tumors, the strong tumor inhibiting potential of the antiprogesterins cannot be explained by a classical anti-hormonal mechanism. Surprisingly, the antitumor activity is evident in spite of elevated serum levels of ovarian and pituitary hormones. It was established by morphometric procedures that treatment with Onapristone triggers differentiation of the mitotically active polygonal tumor epithelial cell towards secretory active glandular structures and acini. All our quantitative light and electron microscopic data indicate that the antitumor action of antiprogesterins is



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**Dominant-negative interference of the transforming growth factor beta type II receptor in mammary gland epithelium results in alveolar hyperplasia and differentiation in virgin mice.**

Gorska AE, Joseph H, Derynck R, Moses HL, Serra R.

*Cell Growth Differ.* 1998 Mar;9(3):229-38.

Department of Cell Biology and The Vanderbilt Cancer Center,  
Vanderbilt University School of Medicine, Nashville, Tennessee  
37232-2175, USA.

Transforming growth factor (TGF)-beta1 and TGF-beta3 are normally expressed at high levels in the mammary gland during quiescence and at all stages of development, except lactation. Exogenously added TGF-beta1, -beta2, and -beta3 have been shown to regulate growth and differentiation of mammary epithelial cells in vitro and in vivo. TGF-betas signal through a heteromeric complex of type I and type II serine/threonine kinases. The type II receptor is necessary for ligand binding and growth suppression by TGF-betas. Deletions of the cytoplasmic domains of several kinase receptors known to function in multimeric complexes have been shown to act as dominant-negative mutations. To evaluate the role of endogenous TGF-betas in the growth and differentiation of the mammary gland in vivo, we have targeted expression of a truncated, kinase-defective TGF-beta type II receptor to mammary epithelial cells in transgenic mice using the mouse mammary tumor virus promoter/enhancer. Transgene expression was localized to the epithelial cells of terminal ducts and alveolar buds. At approximately 20 weeks of age, virgin female transgenic mice demonstrated varying degrees of mammary epithelial hyperplasia. Mammary glands from transgenic, virgin animals exhibited alveolar development and expression of the milk protein, beta-casein. The data suggest that impaired responsiveness in the epithelium to endogenous TGF-betas results in inappropriate alveolar development and